Ex vivo-expanded human CD19+CD73−CD25+CD71+TIM-1+ B regulatory cells can prolong allograft survival in a humanized mouse model of skin transplantation and are dependent on TIM-1-mediated regulation of STAT3 signaling


The importance of B regulatory cells (Breg) in both health and disease has rapidly become evident over the last decade. Breg are able to control immune responses in animal models of transplantation, and human Breg have been identified in tolerant, kidney transplant recipients. Excessive regulation by Breg may contribute to the development of carcinoma and severe infection. Despite the successful expansion of mouse Breg, the rarity of human Breg in peripheral blood and difficulties with characterisation mean that in vivo investigation and the potential for human Breg as a clinical therapy in transplantation remain elusive.

We report, for the first time, ex vivo expansion of human B cells with in vivo regulatory function (expBreg). expBreg expressed a phenotype associated with endogenous human Breg in peripheral blood, CD19+CD73−CD25+CD71+, and were TIM-1+. We characterize a novel mechanism by which TIM-1 regulates downstream STAT3 signaling within expBreg cells, thus modulating suppressive function. Furthermore, a significant increase in CD19+CD73 CD25+CD71+TIM-1+ B cells was identified in peripheral blood of human subjects with cutaneous squamous cell carcinoma, unlike other human Breg subsets, when compared to healthy controls.

Human CD19+CD73−CD25+CD71+TIM-1+ B cells with regulatory function can be generated ex vivo and can prolong graft survival in a complex, biological environment. This potent suppressor population may represent a novel cellular therapy that could be used alone or as an adjunct to other immunosuppressive regimens to prolong allograft survival in transplantation. Moreover, targeting human Breg may offer new opportunities for reactivating the immune response in patients with cancer.